REMARKS

Claims 27, 30, 31, 60, 61, 64-74, 79-83, and 86 are pending in the present application. The specification at page 3, as well as claim 60 and 61, are amended to correct the spelling of "allogeneic" and "xenogeneic." The specification at page 26 is amended to correct a typographical error. Claim 27 has been amended to specify secretion as well as production, and to specify that the cells can store and secrete insulin. Claims 64, 65, 67, 69 and 71 have been amended to recite "secretion" rather than "expression." Claim 66 has been amended to specify that it is the pancreatic beta cell form of glucokinase. Support for these amendments can be found throughout the application as filed, including at page 3, lines 1-13; page 6, lines 14-22; page 6, line 34-page 7, line 7; and page 19, line 21. No new matter has been added.

Applicants acknowledge the Examiner's withdrawal of the previously pending rejection under 112, first paragraph.

Claim Rejections: 35 U.S.C. § 112:

Claims 27, 30, 31, 60, 61, 64-74, 79-83, and 86 are rejected for allegedly lacking enablement.

Summary of Applicant's Response

1. The Examiner argues that achieving "proper regulation" (Office action, page 3), "faithfully mimic[king] the properties of this highly differentiated secretory cell" (Office action, page 3), and providing an "ideal surrogate cell" (Office action, page 4) are not enabled. The Examiner concludes that providing "regulated insulin secretion" is not enabled (Office action, page 5).

2. The claims, however, do not require mimicking β cells to produce the sort of insulin expression provided by healthy, functioning β cells. The claims have been amended to focus on the invention.

3. The cells used in the claimed methods provide, at the very least, a basal level of insulin secretion *in vivo*. The Declaration of Dr. Myra Lipes (the "Declaration"), filed on April

9, provides that basal levels of insulin secretion are useful and indeed therapeutic. The Examiner has not rebutted this declaration.

4. There is no reason to believe that the POMC promoter is the only promoter that can be used to achieve at least basal levels of insulin production. In fact, the Declaration and specification provide evidence that other promoters can also be used, and the Examiner has not provided a reasoned rebuttal of this evidence.

5. It is well within the skill of one in the art to select and test *in vitro* promoters other than the POMC promoter, e.g., those listed in the specification at page 14, lines 14-15, for use in the present methods. Such testing would be no more than routine.

6. At page 2 of the Office action, the Examiner acknowledges that "a method of producing insulin in a subject *in vivo* by introducing into the subject an intermediate lobe pituitary cell comprising a nucleic acid encoding insulin, wherein said nucleic acid is operatively linked to a heterologous control region that encodes the pro-opiomelanocortin (POMC) promoter" is enabled. The specification and Declaration provide examples of other suitable promoters. As such, the methods of the claimed invention are enabled.

7. Furthermore, the full breadth of the claims is enabled. Claim 27, the only independent claim, recites "introducing into the subject an intermediate lobe pituitary cell." Clearly, the specification provides ample guidance on the selection and use of such cells. Claim 27 further specifies that the cells comprise "a nucleic acid sequence encoding insulin." Again, the specification is amply enabling for such nucleic acid sequences. The cells must be "capable of secreting insulin," and the specification clearly enables such cells, see, e.g., the Examples section. Claim 27 recites that the nucleic acid sequence is "operatively linked to a heterologous promoter that directs expression of the nucleic acid sequence in the intermediate lobe pituitary cell." Again, this is fully enabled; the specification includes clear evidence of a working embodiment using the POMC promoter, and includes guidance on the selection of other promoters. Thus, the full scope of the claimed invention is enabled.

8. Even assuming *arguendo* that glucose-sensitive secretion exactly mimicking native β cells is not enabled, which applicants do not agree with, the full scope of the claims is

still enabled, as the law allows a generic claim to cover later-developed refinements. *In re Fisher*, 427 F.2d 833 (C.C.P.A. 1970).

Detailed Response

The Examiner, at page 2 of the Office action, indicated that while the specification is enabling for

> ... a method of producing insulin in a subject *in vivo* by introducing into the subject an intermediary lobe pituitary cell comprising a nucleic acid encoding insulin, wherein said nucleic acid is operatively linked to a heterologous control region that includes the pro-opiomelanocortin (POMC) promoter, [it] does not reasonably provide enablement for the use of cells having other genetic modifications and other promoters.

The Examiner characterized the invention as "a method of producing insulin in a subject *in vivo* by introducing into the subject an intermediary lobe pituitary cell comprising a nucleic acid encoding insulin, wherein said nucleic acid is operatively linked to a heterologous promoter that directs expression of the nucleic acid in the intermediate lobe pituitary cell." Office action, p. 3. Further, the Examiner went on to state that

> The specification fails to provide an enabling disclosure for the use of transgene constructs that do not encode insulin or do not include the POMC promoter because the proper regulation of insulin secretion is critical for successfully carrying out the claimed method. While the specification discusses a variety of strategies for providing glucose-stimulated insulin secretion (e.g., by further providing transgenes that encode glucokinase, ion channels that mediate glucose-stimulated insulin release, GLP-1 and/or GLUT-2), specific guidance for actually achieving regulated insulin release is not provided to the skilled artisan. (Office action, p. 3, emphasis added)

Applicants respectfully traverse.

The Examiner cites a number of references, all of which are said to support her main hypothesis: insulin production in beta cells is very complex. Tight regulation of the timing and amount of insulin secretion are important to the function of natural beta cells, and those investigators who seek to treat diabetes and other insulin-related disorders have encountered a number of difficulties in trying to perfectly replicate the biology of the beta cell.

Amended claim 27, from which all pending claims in the application depend, reads as follows:

> 27. A method of producing insulin in a subject in vivo, the method comprising introducing into the subject an intermediate lobe pituitary cell that is capable of secreting insulin and comprises a nucleic acid sequence encoding insulin, the nucleic acid sequence being operatively linked to a heterologous promoter that directs expression of the nucleic acid sequence in the intermediate lobe pituitary cell.

Per 35 U.S.C. §112, paragraph 2, the applicant has the duty and the privilege of drafting claims that particularly point out and distinctly claiming the subject matter that the applicant regards as his invention; it is the applicant's decision as to what the invention is, regardless of what others in the field may consider to be "ideal." It has never been a requirement that an invention, to be patentable, must present a perfect solution to a problem. Indeed, it is well established a patent applicant is entitled to claim her invention generically, when she has described it sufficiently to meet the requirements of Section 112. *Utter v. Hiraga*, 845 F.2d 993, 998, 6 USPQ 2d 1709, 1714 (Fed. Cir. 1988) ("A specification may, within the meaning of 35 U.S.C. §112¶ 1, contain a written description of a broadly claimed invention without describing all species that claim encompasses."); *In re Robins*, 429 F.2d 452, 456-57, 166 USPQ 552, 555 (CCPA 1970) ("[R]epresentative samples are not required by the statute and are not an end in themselves.")

In this case, the goal of the method of claim 27, as laid out in the preamble, is straightforward: to produce insulin in a subject *in vivo*. The claimed methods make use of the fact, discovered by the present inventors, that intermediate lobe pituitary cells have several characteristics that are valuable. First, they can store and secrete large amounts of insulin, enough to cure diabetes. They do not co-secrete harmful substances, and so are not likely to be toxic over time. They are not transformed, and so are not likely to cause tumor growth or cancer. Finally, and most importantly, the inventors have discovered that the intermediate lobe cells are unusual in that they are immune privileged -- they avoid immune system recognition and attack. Given that type 1 diabetes is caused by the autoimmune destruction of insulin-producing β cells and that insulin is a key antigenic target of this autoimmune attack, the identification of a cell

type that can produce sufficient amounts of insulin to cure diabetes yet evade immune recognition and attack is highly desirable and advantageous.

The claims do not require that the cells completely mimic all of the functions of natural beta cells, nor would such be required for "successfully carrying out the claimed method," as the Examiner claims. The engineered cells described in the specification and used in the claimed methods are immunologically protected, and are capable of delivering insulin in vivo to a subject. As Dr. Myra Lipes stated in paragraphs 4 and 5 of her declaration, filed on April 9, 2004, with the applicants' previous reply:

> ...Both constitutive promoters and promoters specific to IL cells were known in the art, can work in the claimed methods, and representative examples are disclosed in the specification. See page 14, lines 5-13, of the specification, where, in addition to the POMC promoter, a representative number of constitutive promoters, such as the CMV and SV-40 early promoters, are disclosed. Note that at page 27, lines 29-32, of the specification, it is shown that CMV promoter directs expression in IL cells. Other constitutive promoters that were routinely used in the art at the time of filing include the JC polyomavirus promoter, and the chicken beta-actin promoter. In addition, IL-specific promoters besides POMC promoter were known, such as the prodynorphin (proDyn) promoter. See, e.g., Naranjo et al. (1991, Neuron 6(4):607-17), describing the proDyn promoter, and Day et al. (1993, Endocrinology 133:2652-2659), describing proDyn gene expression in IL cells. Therefore, a skilled person would have been able to envision the entire class of promoters that are active in IL cells....
>
> ... The experiments described in the specification show that IL cells have the proper prohormone processing machinery to produce and secrete fully processed, mature insulin sufficient to produce a therapeutic effect in a diabetic subject even in the absence of insulin secretion being tightly coupled to serum glucose concentrations. See, for example, the section bridging pages 25 and 26 of the specification, which shows that transplantation of insulin-producing IL cells under the kidney capsule of spontaneously diabetic NOD mice resulted in a significant gain in body weight, complete remission from diabetic symptoms, a return to near-normoglycemia, and insulin levels in a similar range to random insulin levels of non-diabetic control mice. There is absolutely no reason to think that other promoters, including other IL-specific promoters or constitutive promoters, would not work also. Therefore, the claimed methods can be carried out even without a glucose-sensitive promoter. Although the ideal or perfect insulin secreting cell would be glucose-sensitive, this does not mean that there is no place for insulin production that is not regulated by glucose levels. Secretion

of basal levels of insulin also provides therapeutic benefit, e.g., by reducing risk of ketoacidosis that results from absolute insulin deficiency that occurs with Type I diabetes. Furthermore, even the standard treatment for diabetes, the self-administration of exogenous recombinant insulin, is not free of risk of episodes of hypoglycemia or hyperglycemia.

The POMC promoter was selected for the described experiments for the simple reason that the construct was intended to be usable to generate transgenic mice. As this particular POMC promoter construct was shown to drive tissue-specific expression mainly to intermediate lobe pituitary cells in transgenic mice (see Tremblay et al, Proc. Natl. Acad. Sci, USA, 85:8890-8894 (1988)), use of the POMC promoter would restrict the effect of the insulin transgene to only those cells. In the claimed methods, such tissue specificity is not necessary, as the methods include introducing into the subjects cells transfected ex vivo. Indeed, the CMV promoter was used to drive transgene expression in intermediate lobe cells in the data shown in Table 1 and Fig. 5, 6 and 7.

As the Examiner acknowledged, the POMC promoter is not glucose-regulated, and the examples included in the specification demonstrate that glucose sensing is not necessary for the cells to have substantial therapeutic value. Example 6, pp. 26-27, demonstrates that transplantation of pituitary cells, which are wildtype aside from the presence of an insulin transgene driven by the constitutive POMC promoter, clearly leads to a substantial improvement in an animal model of diabetes. Furthermore, as Dr. Lipes points out, basal insulin secretion is not without benefit for the treatment of diabetes, e.g., in avoiding ketoacidosis and preventing diabetic complications such as blindness, neuropathy, and impaired peripheral circulation, among other consequences of long-term increases in insulin levels. For example, many people living with insulin-dependent diabetes do so with the aid of long-acting insulin that has a duration of several hours or even days. Indeed, even with the imprecise tools available today to manage diabetes (including insulin pumps), clinical trials indicate that lowering the mean blood glucose levels of patients significantly reduces the risk for long-term complications (The Diabetes Control and Complications Trial Research Group, New England J. Med. 329:977-986 (1993)). This occurs despite the fact that these individuals have marked fluctuations in their

blood glucose levels, suggesting that a surrogate beta cell need not necessarily mimic the precise insulin secretory dynamics of the pancreatic beta cell to have a major therapeutic benefit (Zhang, Diabetes Care, 24:1275-79 (2001)).

The law does not require that an invention solve all of the problems associated with a field, e.g., cure diabetes completely, but rather deems patentable inventions that are useful, even those that are only incrementally useful. The method recited in claim 27 provides for the production and secretion of insulin in a subject – thus providing a therapeutic modality that has much in common with the insulin pumps and injection regimes that are presently used. The Examiner's recitation of art that states that it is "essential to have well-regulated secretion," or that "tight control of insulin release is essential to any therapeutic strategy" overstate the situation; the statements in the cited art are nothing more than expressions from an academic research perspective of what an "ideal" therapeutic strategy might entail. If such were indeed the case, the presently-used treatment modalities would be useless, given that the pumps and injections provide imperfect coupling between insulin secretion and glucose levels. Though it might be "ideal" to have tight coupling, a solution that ameliorates the symptoms of a disease is useful, even though it may not provide an answer to all of the difficulties that are associated with the treatment of the disease. For example, Couzin, News Focus: Islet Transplants Face Test of Time, Science 306:34-37 (2004), at page 35, in discussing the issues facing primary beta cell transplantation therapies, states that

> Increasingly, however, transplanters are wondering whether insulin independence, a goal pushed heavily by islet-transplantation centers, funders, and many patients, is the only yardstick by which to measure islet-transplant success. **Patients ... who have gone back on insulin [after partial failure of an islet transplant] have found that partial islet function can stave off the hypoglycemia they experienced before their transplants.** This has doctors hoping that islet transplants might prevent long-term complications of diabetes, even if recipients still need insulin. (*emphasis added*)

Furthermore, as described in the specification, an *in vivo* animal model of diabetes (the NOD mouse, commonly considered to be a reasonable facsimile of autoimmune diabetes), when

treated with intermediate pituitary lobe cells secreting insulin in a non-glucose regulated manner, demonstrated marked improvement in clinically relevant parameters of disease.

Limiting the claims to the POMC promoter improperly limits the scope of the claims and does not reflect the appropriate breadth of the claimed invention. Per Dr. Lipes' declaration cited above, many other promoters were available to one of skill in the art, and there is no reasonable basis for believing that any number of other promoters would not function in the claimed methods in substantially the same manner as the POMC promoter. The Examiner has provided no evidence to the contrary, and the cited references do not provide evidence that contradicts Dr. Lipes' statement in any way. Indeed, the disclosed cells have characteristics that address some of the very difficulties referred to in those references. For example, as noted above, these cells are immune privileged, thus addressing a major difficulty in the use of transplantation-based therapies. Halban et al., Diabetes 50:2171-2191 (2003), cited by the Examiner, note that "exposing a young child to a lifetime of immunosuppression in order to "cure" diabetes by transplantation is not acceptable" (see page 2182). As the disclosed cells are immune privileged, their use likely obviates the need for life-long treatment with anti-rejection drugs whose toxicity is a major barrier for the widespread clinical applicability of islet transplantation (see Couzin, (2004), *supra*). The Examiner cited the statement in Welsh, 2000, that

> [u]nfortunately none of these cells respond to glucose with physiological secretion of insulin. Indeed, it is only possible to achieve regulation of insulin gene transcription by using promoter constructs that respond to glucose. Because transcription is a much slower process than regulated release from secretory granules, there is a substantial risk of the insulin production getting our of phase with fluctuations in glucose levels leading to episodes of severe hypoglycemia. Thus, the generation of a substitute β-cell from non-β cells may prove to be exceedingly difficult.

However, this is simply not relevant to the claimed methods; the cells used in the method of independent claim 27, without any additional manipulation, are capable of synthesizing mature, active insulin, storing it in granules, and releasing it. Glucose-sensitive transcription is not

required in the cells recited in the method of claim 27, thus the dangers and difficulties articulated in Welsh are not relevant to the method claimed therein.

The methods of claims 64-73 as amended include the use of cells that comprise proteins that control secretion of insulin in response to glucose. A number of such proteins are described in the specification, and, given the guidance provided by the specification and the level of skill in the art, it would be a matter of routine for a skilled practitioner to co-express such proteins in the cells used in the method of claim 27. As described in the specification, the disclosed intermediate pituitary lobe cells can express mature, active insulin, and they have the appropriate secretion apparatus and are capable of expressing and constitutively secreting sufficient amounts of insulin to cure diabetes in an animal model of diabetes, but not so much as to cause insulin toxicity in the animals. To regulate this secretion in response to glucose, the expression of additional proteins may be required. The cellular machinery required for controlled secretion is relatively well-understood, and the specification as filed discloses a number of these proteins, e.g., glucokinase, K+ and Ca++ ion channels, GLP-1 and GLUT-2, see pages 12-19. Indeed, it has been shown by Motoyoshi and colleagues that glucose sensing capabilities in the physiological glucose range could be introduced into insulin-producing the AtT-20 anterior lobe pituitary cell line by the simple cotransfection of glucokinase and GLUT2 genes (Motoyoshi et al., Diabetologia 41:1492-1501 (1998)). Thus, it would have been well within the ability of a skilled practitioner, given the guidance present in the specification and the high level of skill in the art, to select one or more of these proteins and express them in an intermediate lobe pituitary cell, as claimed. Alone and in combination with the state of the art at the time of filing, the specification provides more than sufficient guidance to enable one of skill in the art to use the claimed methods to achieve constitutive and glucose-stimulated secretion.

Applicants note that the presence of inoperative embodiments within the scope does not necessarily render a claim non-enabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir.

1984) (prophetic examples do not make the disclosure non-enabling). Furthermore, a claim can dominate yet-to-be-invented improvements. "It is apparent that such an inventor should be allowed to dominate the future patentable inventions of others where those inventions were based in some way on his teachings. Such improvements, while unobvious from his teachings, are still within his contribution, since the improvement was made possible by his work." *In re Fisher,* 427 F.2d 833, 839 (C.C.P.A. 1970). Thus, even if embodiments in which the "ideal" is achieved, i.e., perfect mimicry of a normal, functioning beta cell, are not presently enabled (which applicants do not agree with) but are part of future refinements, the fact that the present claims could cover such embodiments does not render the present claims non-enabled. The present claims are drawn to methods for producing and secreting insulin in a subject *in vivo*, and do not explicitly recite methods of treating diabetes. Applicants submit that the full scope of every pending claim is enabled; one of skill in the art would be able to make and use the claimed invention, without undue experimentation, given the guidance in the specification and the level of skill in the art.

For at least the above reasons, applicants submit that the claims as amended are enabled, and request withdrawal of the rejection thereto.

Applicants submit that the claims as amended are patentable and request rapid notification of allowance.

Enclosed is a check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

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